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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 22

Application Number: 09/447,681
Filing Date: November 23, 1999
Appellant(s): ROTH, JACK A.

Gina N. Shishima
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 7, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences, which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 67 and 86-89 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Liu et al. Growth Suppression of Head and Neck Cancer Cells by the Introduction of a Wild-Type *p53* Gene Via a Recombinant Adenovirus. Cancer Res. 1994, Volume54, pages 3662-3667.

Chen et al. Genetic Mechanisms of Tumor Suppression by the Human p53 Gene. Science. 14 December 1990, Volume 250, pages 1576-1579.

Stratford-Perricaudet et al. Evaluation of the Transfer and Expression in Mice of an Enzyme-Encoding Gene Using a Human Adenovirus Vector. Human Gene Therapy. 1990, Volume 1, pages 241-256.

Wilkinson et al. Constitutive and Enhanced Expression from the CMV Major IE Promoter in a Defective Adenovirus Vector. (1992) Nucleic Acids Res. 20, 2233-2239.

Colicos et al. Construction of a Recombinant Adenovirus Containing the *denV* Gene from Bacteriophage T4 which can Partially Restore the DNA Repair Deficiency in Xeroderma Pigmentosum Fibroblasts. Carcinogenesis. 1991, Volume 12, pages 249-255.

Rajan et al. Simian Virus 40 Small t does not Transactivate RNA Polymerase II Promoters in Virus Infection. J. Virol. 1991, Volume 65, pages 6553-6561.

Hitt et al. Adenovirus E1A Under the Control of Heterologous Promoters: Wide Variation in E1A Expression Levels has Little Effect on Virus Replication. Virol. 1990, Volume 179, pages 667-678.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

As appellant has filed terminal disclaimer over US patent application 09/668,532 (now US Patent 6,511,847) and US Patent 6,410,010, the obviousness-type double patenting rejections have been overcome. Appellant's arguments regarding this rejection are moot, and not addressed.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 67 and claims 86-89 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record as set forth in the office action mailed September 27, 2002 in paper no. 19.

The instant specification does not contemplate adenoviral vectors comprising a wild type p53 gene operably linked to a promoter, nor does the specification contemplate the specific embodiments where the promoter is a CMV, RSV, β-actin or SV40 promoter. Thus, the specification does not provide evidence that Appellant had possession of the claimed invention at the time of filing.

The specification has been read in its entirety and the examiner has not been able to determine support that would satisfy the written description portion of 35 USC §112. Further, a reading of the specific citations indicated by Appellant in the preliminary amendment filed November 23, 1999 to support the present claims, reveals that support is not found at these citations. At page 7, lines 1-7, there is discussion of evidence in the art that mutations of the p53 gene cause lung cancer; page 9, line 6-8, states that the vector construct for introducing a wild type p53 gene under the control of a β-actin promoter is a retroviral vector; page 9, lines 14-15, discusses in general wild type p53 constructs; page 14, lines 26-27 and 31-34, discusses antisense RNA expressed from any promoter; page 15, lines 1-5,

state that the β-actin, RSV, SV40 and a CMV promoters are used to express antisense RNA; page 25, lines 4-5, discuses that mutations of a p53 gene are the most frequently found mutations in human cancers; page 26, lines 13-16, states that the inventors feel that the reversal of a single altered genetic event in a cancer cells can potential reverse critical features of the malignant phenotype; page 27, lines 24-28, states that the protocol focuses on the regional delivery of wild type p53 for the treatment of tumors; page 33, lines 9-11, states that adenovirus can be used to introduce an antisense intron; and page 66, lines 10-18, states that tumors should be resected and that to the residual tumor the appropriate retroviral vector is to be injected. Further, the examiner has found at page 63, lines 30-34, a statement that antisense p53 in a retrovirus is used; page 64, lines 27-31, states a retroviral construct comprising p53 cDNA; page 65, lines 7-22, states retrovirus mediated transfer of p53 cDNA and pages 67, line 15 to page 68, line 1, states risks of retroviruses. At no place in the specification is the invention of the claims clearly set forth so that the skilled artisan would realize that which Appellant perceived as their invention at the time of filing. In the places where adenovirus or the specific classes of promoters claimed are disclosed, each such disclosure is within the context of antisense RNA production. Therefore the specification lacks a written description of the invention as claimed.

MPEP 2163.02 states:

> Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., Vas-Cath, Inc. v.Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Electronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); Amgen, Inc. v. Chugai Pharmaceutical, 927

> F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). The subject matter of the claim need not be described literally (i.e., using the same terms or in haec verba) in order for the disclosure to satisfy the description requirement. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

It is maintained that the present specification provides no such reasonable clarity to those skilled in the art that Appellant was in possession of the claimed invention.

Appellant is denied benefit of the early priority dates claimed, as they do not provide a written description of the claimed invention. To be granted priority under 35 USC § 120, the claims must comply with 35 USC § 112, first paragraph. The specifications of 07/960,513, filed October 13, 1992 and 07/665,538, filed March 6, 1991 do not provide written description for claimed adenoviral vectors. Therefore, appellant is given the priority date of November 23, 1999.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 67 and 86 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Liu et al (1994) Cancer Res. 54, pages 3662-3667.

Lui teaches an adenovirus vector comprising a wild-type p53 gene operably linked to an CMV promoter (page 3662, col. 2, parag. 4). Thus, Lui clearly anticipates the claimed invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious

at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 86-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (1990) Science 250, 1576-1579 and Stratford-Perricaudet et al (1990) Human Gene Therapy 1, 241-256 in view of Wilkinson et al (1992) Nucleic Acids Res. 20, 2233-2239, Colicos et al (1991) Carcinogenesis 12, 249-255, Rajan et al (1991) J. Virol. 65, 6553-6561 and Hitt et al (1990) Virol. 179, 667-678.

Claims 86-89 are drawn to adenovirus vectors comprising a wild type p53 gene or a human wild type p53 gene under the control of a promoter, where the promoter can be a CMV promoter, a β-actin promoter, an SV40 promoter or an RSV promoter.

Chen et al teach retroviral vectors comprising a wild type human p53 operably linked to the retroviral LTR (page 1576, col. 3, Figure 1). Chen et al teach that wild type 53 is expressed in transduced Saos cells, and that the transduced cells failed to form colonies on soft agar or tumors in nude mice (page 1577, col. 2, line 12 to col. 3, line 8). Chen et al also teach that wild type p53 counters the transformation phenotype conferred by a mutant p53 when both genes are present in equal gene dosage (page 1579, col. 1, parag. 1 to col. 2, line 1 and col. 2, parag. 1, lines 25-28). Stratford-Perricaudet et al teach the correction of an enzyme deficiency related disorder in mice (abstract). The mice are mutant for ornithine transcarbamylase and when treated with an adenovirus vector comprising an ornithine transcarbamylase DNA sequence operably linked to the adenovirus major late promoter, the mice exhibit a reversal of the mutant phenotype (page 251, parag. 1, lines 1-3). Chen et al and Stratford Perricaudet et al do not teach adenoviral vectors comprised of a wild type p53 gene under the control of a CMV promoter, a β-actin promoter, an SV40 promoter or an RSV promoter. Wilkinson et al teach the production of an adenovirus expression system where a CMV promoter regulates expression of lacZ (page 2234, col. 1, parag. 5, lines 1-3). Wilkinson et al also teach that the adenovirus-CMV system can be used to studies of gene expression and gene regulation (page 2238, col. 2, parag. 4, lines 1-4). Colicos et al teach an adenovirus vector comprising a T4 *denV* gene operably linked to the RSV promoter, the RSV LTR (page 250, col. 1, parags. 4-7, figure 1 and figure 2). The vector, Ad5denV, was shown to partially complement the excision repair deficiency in primary fibroblasts from xeroderma pigmentosa patients (page 254, col. 1, parag. 2,

and page 253, figures 6 and 7, and Table 1). Rajan et al teach an adenoviral vector comprising a cDNA sequence encoding an SV 40 small-t antigen operably linked to an SV40 promoter (page 6554, col. 1, parag. 2). Rajan et al teach that the expression of the SV40 small-t antigen results in the transactivation of adenovirus EII early promoter (page 6557, col. 1, line 13 to col. 2, line 4). Hitt et al teach an adenovirus where the expression of the E1A gene is regulated by a human β-actin promoter (page 670, col. 1, line 12 to col. 2, line 2, and figure 1). Hitt et al teach that E1A production is 3 to 5 times higher than by wild type adenovirus (page 675, col. 2, parag. 1, lines 11-16).

Thus it would have been obvious to the ordinary artisan at the time of the instant invention to determine the reversal of a transformed phenotype by expressing in an adenoviral vector comprising a human wild type p53 gene operably linked to a promoter, and specifically where the promoter is a CMV promoter, a β-actin promoter, an SV40 promoter or an RSV promoter, given the teachings of Chen et al that wild type p53 can reverse the transformed phenotype of tumor cells when the cells are transduced with a retroviral vector comprising a human wild type p53 gene operably linked to a promoter and the teachings of Stratford-Perricaudet et al that adenoviruses are useful for human gene therapy protocols in view of the teachings of Wilkinson et al, Colicos, Rajan et al or Hitt et al that a CMV promoter, a β-actin promoter, an SV40 promoter or an RSV promoter functions within a adenovirus to regulate expression of a sequence encoding a protein of interest. All that is required that there is a reasonable expectation of success and motivation to make the claimed adenovirus vectors. Motivation is provided by Chen et al in stating that expression of p53 in cells Saos cells which lack functional p53 reverts the transformed phenotype, and that such suggests possible clinical use of p53 gene replacement (page 1579, col. 1, parag. 1, line 1 to col. 2, line 1 and col. 2, lines 21-25). Additional motivation comes from Stratford-Perricaudet et al offer that states that adenoviral vectors can be used in human gene therapy procedures to restore impaired metabolism (abstract, last line). Promoter testing was known within the art at the time of filing to determine those promoters that provided the best expression.

(11) Response to Arguments

A. Written Description

Appellant provides seven "bullets" that they feel support the enablement of the present claims. The examiner has read these seven bullets and does not agree with Appellant's reasoning and evidence. The discussion of the seven bullets, referred to as 1-7, in respective order, will provide the examiner's reading of these citations from the specification. (Brief, pages 10-11). Appellant argues that:

1. At page 9, lines 6-12, the specification states generally "in one specific embodiment, the invention concerns vector constructs for introducing wild type p53 genes ..."; "... wherein the wt-p3 is placed under the control of the β-actin promoter, and the unit is positioned in reverse orientation into a retroviral vector." Therefore, this citation discloses a "specific embodiment" of a vector constructs for introducing wild-type p53 into cells, and states "these embodiments involve the preparation of a gene expression unit where the wt-p53 gene is placed under the control of the β-actin promoter, and the unit is positioned in a reverse orientation into a retroviral vector." In this discussion, the only contemplation is stated to be a retroviral vector having in reverse orientation a wt-p53 gene operatively linked to a promoter. There is no contemplation of an adenoviral vector comprising a CMV promoter, or any other specifically claimed promoter, operatively linked to a wt-p53 gene at this place in the specification. Without evidence of contemplation, there is no possession at the time of filing.

2. At page 61, lines 29-30, the only vector discussed to express wild type p53 in both orientations is a retroviral vector. There is no specific disclosure of adenovirus vectors at this citation, and thus there is no evidence provided here that appellant had possession of the claimed invention at the time of filing. Thus, this citation fails to provide the needed support for written description.

3. At page 8, line 25 or page 9, line 4, the effect which is stated to be achievable with other promoter/vector constructs, is the enhanced expression when the promoter in the retrovirus is reversed with regard to other promoters within the retrovirus (page 8, lines 25-31). This citation discusses the discovery that when the selected promoter/gene construct is aligned within the vector in an orientation that is reversed with respect to direction of transcription with respect to other promoters with in the vector,

a dramatic increase in transcription of the selected gene is seen. Then the passage goes on to discuss the use of retroviral vectors where the transcription of the selected gene is in reverse orientation to other retroviral transcription. The passage continues by stating that while the increase in transcription was observed using the β-actin promoter and retroviral vector, the inventors believe that the increase will be seen other promoter/vector constructs. The examiner will agree that Appellant has contemplated in general vectors having the gene of interest operatively linked to promoter, and having both in reverse orientation for transcription relative to transcription of other genes in the vector. However, the support for other than retrovirus does not support the species of adenovirus vector comprising a CMV promoter, or any other promoter. There is no evidence provided at this citation that appellant was in possession of the claimed subject matter at the time of filing.

4. At page 14, lines 21-23, are not seen as supporting written description. A reading of the specification from at least page 5, line 7 to at least page 16, line 10, shows that this citation is embedded in a paragraph discussing antisense technology. This citation does state that "in addition to retroviruses, it is contemplated that other vectors can be employed, including adenovirus ....". However, when read in context of the paragraph, one would realize that the adenovirus contemplated contains antisense sequences. The larger relevant citation (page 14, lines 9-25) states "in broader aspects of the invention, a preferred approach will involve the preparation of retroviral vectors .....", "although the retrovirus would inhibit the growth of the tumor, the expression of the antisense construct in non-tumor cells .....", "in addition to retroviruses, it is contemplated .... adenoviruses" .As discussed above the entire paragraph, page 14, lines 9-25, contemplates only antisense. This only supports an adenoviral vector comprising an antisense construct and not the adenovirus of the claims. Thus, this citation fails to provide evidence of possession of the claimed invention at the time of filing.

5 and 6. At page 15, lines 1-4, and page 14, line 35 to page 15, line 2, each citation is embedded in a paragraph that begins "the particular promoter that is employed to control the expression of the antisense RNA ....". Furthermore, page 15, line 5 states that "while the β-actin promoter is preferred in the invention is by no means limited to this promoter, and one may also mention .....CMV." However, when the entire paragraph is read, "the invention" at this point is the expression of antisense sequences. Please

refer to the paragraph at page 14, line 27 "the particular promoter that is employed to control the expression of the antisense RNA in a vector construct is not believed to be particularly crucial ..... where a human cell is targeted, it will be preferred to position the antisense RNA coding region adjacent to and under the control of a promoter that is capable of being expressed in a human cell ... generally speaking, such a promoter might include either a human cellular or viral promoter..... while the β-actin promoter is preferred .... CMV". Page 14, line 35 to page 15, line 2, states "generally speaking, such a promoter might include either a human cellular or viral promoter.....". However, when read in the full context, as discussed above (page 14, lines 21-23), the description is for "generally speaking" regarding promoters for use in retroviruses comprising antisense sequences, and not the claimed invention. A reading of the complete paragraph assigns the citation provided by Appellant to refer only to retrovirus vectors expressing antisense. There is no written support for the claimed invention.

7. At page 16, lines 5-10, the specification states "while the retrovirus construct aspect .... concerns the use of a β-actin promoter in reverse orientation, there is no limitation on the nature of the selected gene ..."; "thus, the invention concerns the use of antisense coding constructs as well as "sense" constructs that encode a desired proteins. The contemplation is clearly for other genes expressed in the sense or antisense orientation from the β-actin promoter in a retroviral vector. The specification at this point does not discuss adenovirus as a contemplated vector, the CMV promoter as the contemplated promoter or wt-p53 as the contemplated gene. Thus, this citation fails to provide written description of the claimed invention.

The passages provided by Appellant do not provide the type of disclosure that would convey to the artisan that Appellant possessed the claimed invention at the time of filing. The are no passages that clearly provide written description of an adenovirus vector comprising a CMV promoter, a β-actin promoter, an SV40 promoter or an RSV promoter controlling a wt-p53 gene so that the artisan would realize that Appellant considered such as part of the invention at the time of filing.

Appellant argues that they provided during prosecution declarations from Dr. Lou Zumstein and Dr. Philip Hinds, both whom appellant defines as persons of ordinary skill in the art, in support of their allegations that the specification provides written description of the claimed invention (Brief, page 11,

parag. 1, lines 1-3). Appellant argues that evidence, as opposed to argument, should be required to meet the "preponderance of the evidence" standard in MPEP 2163.04 (Brief, page 11, parag. 1, lines 7-8). These arguments are not persuasive.

Both declarants Zumstein and Hinds used as their evidence citations from the specification. These citations both state provide the evidence that the specification provides written description of the claimed invention. The examiner's response used the same evidence as the declarants: the specification. In rebutting the statements made by both declarants, the examiner reviewed the specific citations indicated by the declarants and made an argument as to why those citations did not support written description of the claimed invention. This type of rebuttal is permissible under MPEP 2163.04:

> When a rejection is maintained, any affidavits relevant to the 35 U.S.C. 112, parag. 1, written description requirement, must be thoroughly analyzed and discussed in the next Office action. See In re Alton, 76 F.3d 1168, 1176, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996).

The examiner provided such a thorough analysis.

Appellant argues that adenoviruses are discussed in the application and states that such can be found at specification page 14, lines 9-12, which states "In broader aspects of the invention, a preferred approach will involve the preparation of retroviral vectors which incorporate nucleic acid sequence encoding the desired construct, once introduced into the cell to be treated ..." (Brief, page 12, parag. 1, lines 4-8). Appellant argues that the use of adenovirus is discussed in the context of "broader aspects of the invention" (Brief, page 12, parag. 1, lines 8-10). Appellant argues that retrovirus and antisense constructs are but examples of broader aspects of the invention. Appellant argues that the paragraph at page 14, line 35 to page 15, line 2 recites particular embodiments of the invention such as antisense, but the passage includes "Generally speaking, such a promoter might include either a human cellular of viral promoter.." (Brief, page 12, parag. 1, lines 10-14). These arguments are not persuasive.

The paragraph at page 14, lines 9-25, discusses the invention in terms of delivering antisense oligo nucleotides to a cell using a retroviral vector. The mention of adenovirus in the last sentence of the paragraph, refers to the delivery of antisense oligonucleotides. When the paragraph at page 14, lines 9-25 are read in context, including paragraphs before an after the citation, it is clear that the delivery of

antisense oligonucleotides is the topic. The paragraph at page 13, lines 23-43, discusses the application of antisense intron RNA either directly or indirectly to the cell (lined 25-26). The indirect form of application is by an antisense construct in the form of retroviral constructs (lines 26-28). The remainder of the paragraph discusses the direct delivery of antisense RNA. The next paragraph, which is the one cited by Appellant, continues a discussion of delivery of the construct via a retroviral vectors, which incorporate the desired construct (page 14, lines 9-14). The discussion of construct here clearly refers back to the antisense construct in the preceding paragraph. This is further emphasized by statements made later in the paragraph that the retrovirus would inhibit growth of the tumor cell (page 14, lines 17-18). Then, the paragraph lists other vectors that could be used instead of retrovirus, adenovirus being one of them (page 14, lines 23-24). However, the clear contemplation is the delivery of antisense RNA by these other vectors, including adenovirus. The paragraph bridging pages 14 and 15, is "generally speaking" about promoters for the antisense constructs. The sentence just prior to Appellant's citation states "... it will be preferred to position the antisense RNA coding region adjacent to an under the control of a promoter that is capable of being expressed in a human cell. Generally speaking, such a promoter might include a human cellular or viral promoter." Thus, appellant's citation at page 14, line 35, when read in context, not only indicates that the human cellular and viral promoters are contemplated for expressing antisense RNA, it also adds support that the mention of adenovirus in the preceding paragraph is in the context of expressing antisense RNA and not wild-type p53 or any sense construct.

Therefore, none of appellant's nor declarants citations or arguments thereof provides for written description of an adenoviral vector comprising a wild-type p53 gene at the time of filing. As appellant cannot possess what has not been described, appellant has not shown possession of the claimed invention at the time of filing.

B. Art Rejections

1. Rejection under 35 U.S.C. 102, Lui

Appellant argues that their earliest priority date is October 13, 1992, and thus Lui is a post filing publication and is not available as a prior art document. (Brief, page 13, column 1 and 2). This argument is not persuasive.

For the reasoning presented above, appellant's are not due benefit of their earlier filing dates because the specification lacks written description for the claimed invention. As appellant has been given a priority date of November 23, 1999. This later filing date makes Lui an available reference.

2. Rejection under 35 U.S.C. 103

Appellant argues that the combination of references in the previous office action do not provide the requisite teachings, motivation or suggestions required for obviousness. Appellant argues that the Wilkinson reference does not teach or suggest using adenoviral vectors for gene therapy. Appellant argues that there is no cited evidence that would have considered using adenovirus in a therapeutic context, and thus Chen in view of Wilkinson is improper. Appellant argues that there is no suggestion in any of the cited references that one should substitute the retroviral vector of Chen with the adenoviral vector of Wilkinson. (Brief, page 15, lines 15-20 and page 15, lines 4-7). Appellant argues that the references of Colicos, Rajan and Hitt are cited for the use of an adenoviral vector comprising an RSV promoter, an SV40 promoter or a β-actin promoter, respectively (Brief, page 15, parag. 2, lines 3-5). Appellant argues that each reference discloses an adenoviral vector with a promoter that does not drive expression of a p53 gene (Brief, page 15, parag. 2, lines 5-7). Appellant argues that Chen does not motivate its combination with Wilkinson, Colicos, Rajan or Hitt, and that Wilkinson, Rajan or Hitt do not suggest combination with Chen (page 16, lines 4-7). These arguments are not persuasive.

As cited in the previous office action, mailed September 27, 2002, Stratford-Perricaudet teaches the correction of an enzyme deficiency related disorder in mice treated with an adenovirus vector comprising an ornithine transcarbamylase DNA sequence operably linked to the adenovirus major late promoter, the mice exhibit a reversal of the mutant phenotype (page 251, parag. 1, lines 1-3). This clearly provides the proposal that adenovirus can successfully be used in gene therapy protocols. Further, Wilkinson teaches that the adenovirus-CMV system can be used to studies of gene expression and gene regulation (page 2238, col. 2, parag. 4, lines 1-4). The correction of the transformed phenotype in Saos cells by delivering a wild-type p53 gene in a retroviral vector, requires both gene expression and gene regulation. The claimed product, an adenoviral vector comprising a wild-type p53 gene operably linked to a CMV promoter, is obvious over Chen in view of Wilkinson. Chen has taught a mutant cell - retroviral

expression system in which gene expression and gene regulation is paramount. Wilkinson has taught an adenoviral expression system, and states that this system is useful for studying gene expression and gene regulation. When this is taken in view of Stratford-Perricaudet, the proposal for preparing an adenoviral vector comprising a CMV promoter operably linked to a wild-type p53 gene is obvious under the meaning of 103. Thus, the ordinary artisan would have found it obvious to take the mutant cell - retroviral expression system of Chen and substitute the adenoviral – CMV promoter of Wilkinson to study gene expression and gene regulation in Saos cells for gene therapy protocols. Likewise with references Colicos, Rajan and Hitt. Each is cited showing expression of a gene of interest from an adenoviral vector comprising an RSV promoter, an SV40 promoter or a β-actin promoter, respectively. These teachings in view of Chen teaching the reversal of transformation by expressing wild-type p53 from a retroviral vector and Stratford-Perricaudet teaching successful gene therapy by administering an adenoviral vector expressing a therapeutic protein, provides motivation to combine to study gene expression and gene function. Appellant it is noted has not addressed Stratford-Perricaudet.

Appellant argues that it is impermissible for the examiner to pick and chose from a reference only that which will support a given position to the exclusion of other parts necessary to the full appreciation of what such references fairly suggests to one skilled in the art. (Brief, page 15, parag. 1. This argument is not persuasive as there is no evidence of picking an choosing or what was excluded.

Appellant argues that Wilkinson, Colicos, Rajan and Hitt teach away from the claimed invention because they fail to mention p53, and they discuss expression of other genes, none of which is a therapeutic gene. Appellant argues that several of the genes were thought to be responsible for cellular transformation. (Brief, page 16, parag. 1).

Appellant's arguments might have greater bearing if Stratford-Perricaudet were not of record in the 103. Stratford-Perricaudet, as discussed above, teaches a successful gene therapy protocol where an adenoviral vector delivers a wild-type version of a mutant gene. The references of Wilkinson, Colicos, Rajan and Hitt each teach an adenoviral vectors with, respectively, a gene of interest under the control of a CMV promoter, an RSV promoter, an SV40 promoter and a β-actin promoter. Furthermore, just because none of the secondary references teach the expression of a p53 gene, that is just because none

of the secondary references are a 102-type reference, does not mean that the references teach away from the claimed invention. Further, whatever gene was being expressed in the secondary references does not teach away because use of the references is based on what was being expressed. The rejection clearly indicates substituting the gene of the reference with p53, the gene of Chen. Additionally, teaching away from an invention or an obviousness rejection, means that the art cited provides reasoning or indicates that a particular combination would not function together. None of the cited references teach that an adenovirus of the claims could not function together.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

dc
May 21, 2003

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